

## **REMARKS**

### **I. Introductory Comments**

In the Office Action under reply, the Examiner has made the Restriction Requirement of October 21, 2004 final and has therefore withdrawn the claims from further consideration. In addition, the Examiner has objected to the Specification on the basis of incorrect use of trademarks. Finally, the Examiner indicated that the claims were rejected as follows: under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement (claim 14); under 35 U.S.C. §102(b) as allegedly being anticipated by Minamino et al. (U.S. Patent No. 6,037,452) (claims 1-7, 12-15, 17-22, 24, and 26-30); under 35 U.S.C. §103(a) as allegedly being unpatentable over Minamino et al. (U.S. Patent No. 6,037,452) in view of Davis et al. (U.S. Patent No. 4,179,337) (claims 1, 3-4 and 8-10); under 35 U.S.C. §103(a) as allegedly being unpatentable over Minamino et al. (U.S. Patent No. 6,037,452) in view of Greenwald (U.S. Patent No. 5,298,643) (claims 1, 3-4 and 8-11); under 35 U.S.C. §103(a) as allegedly being unpatentable over Röstin et al. [Röstin et al. (2000) *Bioconjugate Chem.* 11:387-396] in view of Greenwald (U.S. Patent No. 5,298,643) (claims 1, 14 and 16); and under 35 U.S.C. §103(a) as allegedly being unpatentable over Minamino et al. (U.S. Patent No. 6,037,452) in view of Longenecker et al. (U.S. Patent No. 4,994,439) (claims 1, 23 and 25). The rejections are traversed for reasons provided below.

### **II. Amendments to the Specification and Claims**

#### **A. Specification**

As requested by the Examiner, capitalization has been provided for the trademarks used in paragraph [0007] of the Specification. No new matter has been introduced by way of the changes.

#### **B. Claims**

Claims 1-61 were previously pending. Claims 1, 2 and 14 have been amended. Claims 31-61 have been withdrawn without prejudice from further consideration by the Examiner in view of the finality of the Restriction Requirement. Thus, claims 1-30 remain pending and under consideration.

Support for the changes to the claims is identified below. Additional support other than that identified below may exist in the originally filed application for one or more changes to the claims.

Claim 1 has been amended to recite conjugate-comprising compositions "wherein at least about 82% of the conjugates in the composition each has one to three water-soluble polymers covalently attached to a Factor VIII moiety." Support for the change can be found in the Experimental, where for example, at least about 82% (~39% + ~32% + ~11%) of the conjugates in the composition described in Example 6 each has one to three water-soluble polymers attached to a Factor VIII moiety. Other Examples provide support for compositions having percentages of conjugates of one to three water-soluble polymers covalently attached to a Factor VIII moiety higher than 82%; for example, Example 7 discloses a composition wherein 94% of the conjugates have a single polymer attached to a Factor VIII moiety. The remaining changes to claim 1 are believed to improve the readability of the claim.

A period (".") has been added at the end of claim 2 in order to provide correct claim form. See Section 608.01 of the Manual of Patent Examination and Procedure ("M.P.E.P.").

The phrase "biologically active fragments" has been deleted from claim 14.

As support for the changes is found in the application as filed, no new matter is introduced by the entry of the above-identified changes. The changes to the claims are made for clarification purposes only should not be interpreted as acquiescence in any claim rejection.

### **III. The Interview of March 17, 2005**

At the undersigned's request, an interview with the Examiner was conducted on March 17, 2005. During the interview, the propriety of one or more claims rejections was discussed (although no resolution was reached).

### **IV. The Restriction Requirement**

On page 2 of the Office Action, the Examiner maintained the requirement for restriction between Groups I, II, III and IV. The Examiner has indicated that the requirement is final.

Applicants respectfully request reconsideration of the requirement for restriction, based on their prior arguments filed on November 2, 2005. In addition, Applicants reserve their right to petition the Commissioner to review the requirement for restriction, deferring the filing of

such petition until after final action on or allowance of the claims, but not later than appeal. See 37 C.F.R. §1.144.

#### **V. The Objection to the Specification**

The Examiner has objected to paragraph [0007] of the Specification on the basis of incorrect use of trademarks. In response, Applicants have capitalized all trademarks in the paragraph. It is believed that Applicants actions in this regard address the Examiner's objection. Reconsideration and removal of the objection is respectfully requested.

To the extent that further correction is required to remove the objection, the Examiner is respectfully requested to describe such actions in the next communication to Applicants.

#### **VI. The Rejection Under 35 U.S.C. §112, First Paragraph,**

The Examiner has rejected claim 14 under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. Specifically, the Examiner has taken this position in view of claim 14's recitation of the term "biologically active fragments."

As the term "biologically active fragments" is no longer recited in the claim 14, the rejection has been rendered moot. Reconsideration and removal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

#### **VII. The Rejection Under 35 U.S.C. §102(b)**

The Examiner rejected claims 1-7, 12-15, 17-22, 24, and 26-30 under 35 U.S.C. §102(b) as allegedly being anticipated by Minamino et al. (U.S. Patent No. 6,037,452). Ostensibly, the Examiner has taken the position that each and every element of the rejected claims can be found in Minamino et al.

The standard for anticipation is rigorous requiring that every element of the claimed invention be disclosed by a single prior art reference. *See Minnesota Mining & Mfg. Co. v. Johnson & Johnson Orthopaedics, Inc.*, 976 F.2d 1559, 1565 (Fed.Cir.1992); *Scripps*, 927 F.2d at 1576-77; *Lindemann Maschinenfabrik GMBH, v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1458 (Fed.Cir.1984).

Each of the claims requires a composition comprising a plurality of conjugates, wherein at least about 82% of conjugates in the composition each has one to three water-soluble polymers

covalently attached to a Factor VIII moiety. Minamino et al., however, teaches Factor VIII conjugates "containing polyalkylene glycol added to about 50-70% of amino groups in molecules." In native Factor VIII, there are "158 amine-containing lysine residues (6.8 weight percent of the entire protein." See Applicants' specification at paragraph [0107]. Thus, Minamino et al. effectively teaches Factor VIII conjugates (and their corresponding conjugate-containing compositions) comprising about 79-110 (50-70% of 158) polyalkylene glycol polymers attached to Factor VIII.

Because the reference describes compositions comprising conjugates having about 79-110 polyalkylene glycol polymers attached to Factor VIII, Minamino et al. does not teach the claim element of a composition comprising a plurality of conjugates, wherein at least about 82% of conjugates in the composition each has one to three water-soluble polymers covalently attached to a Factor VIII moiety. Consequently, Minamino et al. does not teach each and every element and the anticipation rejection cannot stand. Reconsideration and removal of the rejection under 35 U.S.C. 102(b) for at least the reasons provided above is respectfully requested.

#### **VIII. The First Rejection Under 35 U.S.C. §103(a)**

The Examiner has rejected claims 1, 3-4 and 8-10 under 35 U.S.C. §103(a) as allegedly being unpatentable over Minamino et al. (U.S. Patent No. 6,037,452) in view of Davis et al. (U.S. Patent No. 4,179,337).

The Examiner cites Minamino et al. as disclosing compositions comprising Factor VIII covalently bound to poly(ethylene oxides). The Examiner cites Davis et al. as disclosing biologically active molecules covalently bound to poly(ethylene oxides) with a nominal molecular weight of 10,000 Daltons to 85,000 Daltons. The Examiner concludes it would have been obvious to one of ordinary skill in the art at the time the invention was made to covalently bind Factor VIII to poly(ethylene oxides) with a nominal molecular weight of 10,000 to 85,000 Daltons.

The rejection is respectfully traversed in view of the following remarks.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim

limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

As stated above, *prima facie* obviousness requires all of the claim elements to be taught or suggested by the teachings of the combined references. In this respect, it must be pointed out that Davis et al. does not cure the deficiencies of Minamino et al. described above in Section VII. That is, Davis et al. -- like Minamino et al. -- does not describe conjugate-containing compositions wherein at least about 82% of conjugates in the composition each has one to three water-soluble polymers covalently attached to a Factor VIII moiety.

Specifically, Davis et al. describes utilization of "between 10 and 100, suitably between 15 to 50 moles of polymer per mole of polypeptide." See Davis et al. at column 3, lines 10-13. Further, Davis et al. describes compositions comprising between 10 and 100 polymer moieties per molecule of insulin (Davis et al., claim 5) and enzyme (Davis et al., claim 19). Thus, Davis et al. neither discloses nor suggests conjugate-containing compositions wherein at least about 82% of conjugates in the composition each has one to three water-soluble polymers covalently attached to a Factor VIII moiety.

Moreover, because both cited references appear not only to focus on conjugates having greater than three polymers attached to a peptidic molecule, but also to describe satisfactory results of such conjugates, neither reference suggests or provides any motivation to prepare conjugate-containing compositions wherein at least about 82% of conjugates in the composition each has one to three water-soluble polymers covalently attached to a Factor VIII moiety.

Consequently, as neither Minamino et al. nor Davis et al. teaches or suggests all the claim elements, the third prong of *prima facie* obviousness fails to be satisfied. As a result, the obviousness rejection of claims 1, 3-4 and 8-10 under 35 U.S.C. §103(a) is unsustainable. Reconsideration and withdrawal of the rejection for at least the reasons provided above is respectfully requested.

#### **IX. The Second Rejection Under 35 U.S.C. §103(a)**

The Examiner has rejected claims 1, 3-4 and 8-11 under 35 U.S.C. §103(a) as allegedly being unpatentable over Minamino et al. (U.S. Patent No. 6,037,452) in view of Greenwald (U.S. Patent No. 6,037,452).

The Examiner cites Minamino et al. as disclosing compositions comprising Factor VIII covalently bound to poly(ethylene oxides). The Examiner cites Greenwald as describing Factor VIII covalently bound to poly(ethylene oxides) with a nominal molecular weight of 10,000 Daltons to 85,000 Daltons. The Examiner concludes it would have been obvious to one of ordinary skill in the art at the time the invention was made to covalently bind Factor VIII to poly(ethylene oxides) with nominal molecular weights of 53,000 to 75,000 Daltons.

The rejection is respectfully traversed in view of the following remarks.

The three criteria for establishing a *prima facie* case of obviousness have been set forth in Section VIII, above.

Again, it is clear that the Examiner cannot satisfy the third requirement of *prima facie* obviousness -- that the prior art reference (or references when combined) teach or suggest all the claim limitations.

As pointed out above in Section VIII, Minamino et al. neither discloses nor suggests conjugate-containing compositions wherein at least about 82% of conjugates in the composition each has one to three water-soluble polymers covalently attached to a Factor VIII moiety.

With respect to Greenwald, this reference describes reacting aryl imidate activated polyalkylene oxide with  $\epsilon$ -NH<sub>2</sub> moieties of lysines and that "the degree of conjugation is limited only by the number of  $\epsilon$ -NH<sub>2</sub> moieties of lysines." See Greenwald at column 8, lines 4-15. Again, given the 158 amine-containing lysine residues in native Factor VIII (see Applicants' specification at paragraph [0107]) it is clear that Greenwald describes compositions of conjugates wherein each conjugate has a relatively large number of polymers attached to a protein or polypeptide. Thus, Greenwald neither discloses nor suggests conjugate-containing compositions wherein at least about 82% of conjugates in the composition each has one to three water-soluble polymers covalently attached to a Factor VIII moiety.

Consequently, as neither Minamino et al. nor Greenwald teaches or suggests all the claim elements, the third prong of *prima facie* obviousness fails to be satisfied. As a result, the obviousness rejection of claims 1, 3-4 and 8-11 under 35 U.S.C. §103(a) is unsustainable. Reconsideration and withdrawal of the rejection for at least the reasons provided above is respectfully requested.

**X. The Third Rejection Under 35 U.S.C. §103(a)**

The Examiner has rejected claims 1, 14 and 16 under 35 U.S.C. §103(a) as allegedly being unpatentable over Röstin et al. [Röstin et al. (2000) *Bioconjugate Chem.* 11:387-396] in view of Greenwald (U.S. Patent No. 6,037,452).

The Examiner cites Röstin et al. as describing B-domain deleted Factor VIII covalently bound to poly(ethylene oxides) with a nominal molecular weight of 5,000 Daltons. The Examiner, however, acknowledges Röstin et al. fails to describe B-domain deleted Factor VIII covalently bound to poly(ethylene oxides) with a nominal molecular weight of higher than 5,000 Daltons. The Examiner cites Greenwald as describing Factor VIII covalently bound to poly(ethylene oxides) with a nominal molecular weight of 10,000 Daltons to 85,000 Daltons. The Examiner concludes it would have been obvious to one of ordinary skill in the art at the time the invention was made to covalently bind Factor VIII to poly(ethylene oxides) with nominal molecular weight higher than 5,000 Daltons.

The rejection is respectfully traversed in view of the following remarks.

The three criteria for establishing a *prima facie* case of obviousness have been set forth in Section VIII, above.

Again, it is clear that the Examiner cannot satisfy the third requirement of *prima facie* obviousness -- that the prior art reference (or references when combined) teach or suggest all the claim limitations.

Here, Röstin et al. describes the preparation of several compositions of conjugates. Each of Röstin et al.'s described compositions of conjugates prepared using polymers having molecular weights of 5,000 Daltons (the molecular weight closest to the claimed range of greater than 5,000 Daltons to 150,000 Daltons) are shown to have degrees of modification greater than three. See the combined pools for mPEG(5000)SS (conjugates 7 and 8), mPEG(5000)SS (conjugates 9 and 10), mPEG(5000)TRES (conjugates 11 and 12), mPEG(5000)TRES (conjugates 13 and 14), and mPEG(5000)TRES (conjugates 15 and 16) in Table 2. Thus, Röstin et al. neither discloses nor suggests conjugate-containing compositions wherein at least about 82% of conjugates in the composition each has one to three water-soluble polymers covalently attached to a Factor VIII moiety, particularly when the polymer has nominal average molecular weight in the range of greater than 5,000 Daltons to about 150,000 Daltons.

As pointed out above in Section IX, Greenwald describes compositions of conjugates wherein each conjugate has a relatively large number of polymers attached to a protein or polypeptide. Thus, assuming *arguendo*, that one of ordinary skill in the art would be motivated to combine the cited references as suggested by the Examiner, the combination of Röstin et al. and with Greenwald would still result in a conjugate-containing composition wherein the conjugates in the composition would have greater than three water-soluble polymers covalently attached to a Factor VIII moiety. In contrast, the claims require conjugate-containing compositions wherein at least about 82% of conjugates in the composition each has one to three water-soluble polymers covalently attached to a Factor VIII moiety, and further wherein each water-soluble polymer has a nominal average molecular weight in the range of greater than 5,000 Daltons to about 150,000 Daltons.

Consequently, as neither Röstin et al. nor Greenwald teach or suggest all the claim elements, the third prong of *prima facie* obviousness fails to be satisfied. As a result, the obviousness rejection of claims 1, 14 and 16 under 35 U.S.C. §103(a) is unsustainable. Reconsideration and withdrawal of the rejection for at least the reasons provided above is respectfully requested.

#### **XI. The Fourth Rejection Under 35 U.S.C. §103(a)**

The Examiner has rejected claims 1, 23 and 25 under 35 U.S.C. §103(a) as allegedly being unpatentable over Minamino et al. (U.S. Patent No. 6,037,452) in view of Longenecker et al. (U.S. Patent No. 4,994,439).

The Examiner cites Minamino et al. as disclosing compositions comprising Factor VIII covalently bound to poly(ethylene oxides). The Examiner cites Longenecker et al. as describing compositions comprising Factor VIII, a polyethylene oxide, and a pharmaceutical excipient that are lyophilized.

The rejection is respectfully traversed in view of the following remarks.

The three criteria for establishing a *prima facie* case of obviousness have been set forth in Section (V), above.

Again, it is clear that the Examiner cannot satisfy the third requirement of *prima facie* obviousness -- that the prior art reference (or references when combined) teach or suggest all the claim limitations.



As pointed out above in Section VIII, Minamino et al. neither discloses nor suggests conjugate-containing compositions wherein at least about 82% of conjugates in the composition each has one to three water-soluble polymers covalently attached to a Factor VIII moiety

With respect to Longenecker et al., Longenecker et al. is completely silent with respect to compositions containing any conjugates.

Thus, as neither Minamino et al. nor Longenecker et al. teaches or suggests all the claim elements, the third prong of *prima facie* obviousness fails to be satisfied. As a result, the obviousness rejection of claims 1, 23 and 25 under 35 U.S.C. §103(a) is unsustainable. Reconsideration and withdrawal of the rejection for at least the reasons provided above is respectfully requested.

## **XII. The Information Disclosure Statement**

Applicants include herewith a 2<sup>nd</sup> Supplemental Information Disclosure Statement and related 1449 forms ("IDS") listing additional references. To the extent that any of references cited in this IDS represent prior art, the pending claims are believed to be patentably distinguishable over each of the references, either alone or in any combination with any other reference in this IDS or previously made of record. Applicants respectfully request the Examiner consider each of the references and provide the undersigned an initialed copy of the IDS forms to thereby indicate each of the references were, in fact, considered by the Examiner.

## **XIII. Conclusion**

In view of the foregoing, Applicants submit that the pending claims satisfy the requirements of patentability and are therefore in condition for allowance. Reconsideration and withdrawal of all objections and rejections is respectfully requested and a prompt mailing of a Notice of Allowance is earnestly solicited.

If a telephone conference would expedite the prosecution of the subject application, the Examiner is requested to call the undersigned at (650) 620-5506.

Respectfully submitted,  
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